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From **a Few Genes, Life's Myriad Shapes**

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Since its humble beginnings as a single cell, life has evolved into a spectacular array of shapes and sizes, from tiny fleas to towering Tyrannosaurus rex, from slow-soaring vultures to fast-swimming swordfish, and from modest ferns to alluring orchids. But just how such diversity of form could arise out of evolution's mess of random genetic mutations -- how a functional wing could sprout where none had grown before, or how flowers could blossom in what had been a flowerless world -- has remained one of the most fascinating and intractable questions in evolutionary biology.

Now finally, after more than a century of puzzling, scientists are finding answers coming fast and furious and from a surprising quarter, the field known as evo-devo. Just coming into its own as a science, evo-devo is the combined study of evolution and development, the process by which a nubbin of a fertilized egg transforms into a full-fledged adult. And what these scientists are finding is that development, a process that has for more than half a century been largely ignored in the study of evolution, appears to have been one of the major forces shaping the history of life on earth.

For starters, evo-devo researchers are finding that the evolution of complex new forms, rather than requiring many new mutations or many new genes as had long been thought, can instead be accomplished by a much simpler process requiring no more than tweaks to already existing genes and developmental plans. Stranger still, researchers are finding that the genes that can be tweaked to create new shapes and body parts are surprisingly few. The same DNA sequences are turning out to be the spark inciting one evolutionary flowering after another. "Do these discoveries blow people's minds? Yes," said Dr. Sean B. Carroll, biologist at the Howard Hughes Medical Institute at the University of Wisconsin, Madison. "The first response is 'Huh?' and the second response is 'Far out.' "

"This is the illumination of the utterly dark," Dr. Carroll added.

The development of an organism -- how one end gets designated as the head or the tail, how feet are enticed to grow at the end of a leg rather than at the wrist -- is controlled by a hierarchy of genes, with master genes at the top controlling a next tier of genes, controlling a next and so on. But the real interest for evolutionary biologists is that these hierarchies not only favor the evolution of certain forms but also disallow the growth of others, determining what can and cannot arise not only in the course of the growth of an embryo, but also over the history of life itself.

"It's been said that classical evolutionary theory looks at survival of the fittest," said Dr. Scott F. Gilbert, a developmental biologist at Swarthmore College. By looking at what sorts of organisms are most likely or impossible to develop, he explained, "evo-devo looks at the arrival of the fittest."

Charles Darwin saw it first. He pointed out well over a century ago that developing forms of life would be central to the study of evolution. Little came of it initially, for a variety of reasons. Not least of these was the discovery that perturbing the process of development often resulted in a freak show starring horrors like bipedal goats and insects with legs growing out of their mouths, monstrosities that seemed to shed little light on the wonders of evolution.

But the advent of molecular biology reinvigorated the study of development in the 1980s, and evo-devo quickly got scientists' attention when early breakthroughs revealed that the same master genes were laying out fundamental body plans and parts across the animal kingdom. For example, researchers discovered that genes in the Pax6 family could switch on the development of eyes in animals as different as flies and people. More recent work has begun looking beyond the body's basic building blocks to reveal how changes in development have resulted in some of the world's most celebrated of evolutionary events.

In one of the most exciting of the new studies, a team of scientists led by Dr. Cliff Tabin, a developmental biologist at Harvard Medical School, investigated a classic example of evolution by natural selection, the evolution of Darwin's finches on the Galapagos Islands.

Like the other organisms that made it to the remote archipelago off the coast of Ecuador, Darwin's finches have flourished in their isolation, evolving into many and varied species. But, while the finches bear his name and while Darwin was indeed inspired to thoughts of evolution by animals on these islands, the finches left him flummoxed. Darwin did not realize for quite some time that these birds were all finches or even that they were related to one another.

He should be forgiven, however. For while the species are descendants of an original pioneering finch, they no longer bear its characteristic short, slender beak, which is excellent for hulling tiny seeds. In fact, the finches no longer look very finchlike at all. Adapting to the strange new foods of the islands, some have evolved taller, broader, more powerful nut-cracking beaks; the most impressive of the big-beaked finches is Geospiza magnirostris. Other finches have evolved longer bills that are ideal for drilling holes into cactus fruits to get at the seeds; Geospiza conirostris is one species with a particularly elongated beak.

But how could such bills evolve from a simple finch beak? Scientists had assumed that the dramatic alterations in beak shape, height, width and strength would require the accumulation of many chance mutations in many different genes. But evo-devo has revealed that getting a fancy new beak can be simpler than anyone had imagined.

Genes are stretches of DNA that can be switched on so that they will produce molecules known as proteins. Proteins can then do a number of jobs in the cell or outside it, working to make parts of organisms, switching other genes on and so on. When genes are switched on to produce proteins, they can do so at a low level in a limited area or they can crank out lots of protein in many cells.

What Dr. Tabin and colleagues found, when looking at the range of beak shapes and sizes across different finch species, was that the thicker and taller and more robust a beak, the more strongly it expressed a gene known as BMP4 early in development. The BMP4 gene (its abbreviation stands for bone morphogenetic protein, No. 4) produces the BMP4 protein, which can signal cells to begin producing bone. But BMP4 is multitalented and can also act to direct early development, laying out a variety of architectural plans including signaling which part of the embryo is to be the backside and which the belly side. To verify that the BMP4 gene itself could indeed trigger the growth of grander, bigger, nut-crushing beaks, researchers artificially cranked up the production of BMP4 in the developing beaks of chicken embryos. The chicks began growing wider, taller, more robust beaks similar to those of a nut-cracking finch.

In the finches with long, probing beaks, researchers found at work a different gene, known as calmodulin. As with BMP4, the more that calmodulin was expressed, the longer the beak became. When scientists artificially increased calmodulin in chicken embryos, the chicks began growing extended beaks, just like a cactus driller.

So, with just these two genes, not tens or hundreds, the scientists found the potential to recreate beaks, massive or stubby or elongated.

"So now one wants to go in a number of directions," Dr. Tabin said. "What happens in a stork? What happens in a hummingbird? A parrot?" For the evolution of beaks, the main tool with which a bird handles its food and makes its living, is central not only to Darwin's finches, but to birds as a whole.

BMP4's reach does not stop at the birds, however.

In lakes in Africa, the fish known as cichlids have evolved so rapidly into such a huge diversity of species that they have become one of the best known evolutionary radiations. The cichlids have evolved in different shapes and sizes, and with a variety of jaw types specialized for eating certain kinds of food. Robust, thick jaws are excellent at crushing snails, while longer jaws work well for sucking up algae. As with the beaks of finches, a range of styles developed.

Now in a new study, Dr. R. Craig Albertson, an evolutionary biologist at Syracuse University, and Dr. Thomas D. Kocher, a geneticist at the University of New Hampshire, have shown that more robust-jawed cichlids express more BMP4 during development than those with more delicate jaws. To test whether BMP4 was indeed responsible for the difference, these scientists artificially increased the expression of BMP4 in the zebrafish, the lab rat of the fish world. And, reprising the beak experiments, researchers found that increased production of BMP4 in the jaws of embryonic zebrafish led to the development of more robust chewing and chomping parts.

And if being a major player in the evolution of African cichlids and Darwin's finches -- two of the most famous evolutionary radiations of species -- were not enough for BMP4, Dr. Peter R. Grant, an evolutionary biologist at Princeton University, predicted that the gene would probably be found to play an important role in the evolution of still other animals. He noted that jaw changes were a crucial element in the evolution of lizards, rabbits and mice, among others, making them prime candidates for evolution via BMP4.

"This is just the beginning," Dr. Grant said. "These are exciting times for us all."

Used to lay out body plans, build beaks and alter fish jaws, BMP4 illustrates perfectly one of the major recurring themes of evo-devo. New forms can arise via new uses of existing genes, in particular the control genes or what are sometimes called toolkit genes that oversee development. It is a discovery that can explain much that has previously been mysterious, like the observation that without much obvious change to the genome over all, one can get fairly radical changes in form.

"There aren't new genes arising every time a new species arises," said Dr. Brian K. Hall, a developmental biologist at Dalhousie University in Nova Scotia. "Basically you take existing genes and processes and modify them, and that's why humans and chimps can be 99 percent similar at the genome level."

Evo-devo has also begun to shine a light on a phenomenon with which evolutionary biologists have long been familiar, the way in which different species will come up with sometimes jaw-droppingly similar solutions when confronted with the same challenges.

Among the placental mammals of the Americas and the marsupials of Australia, for example, have evolved the same sorts of animals independently: beasts that burrowed, loping critters that grazed, creatures that had long snouts for eating ants, and versions of wolf.

In the same way, the cichlids have evolved pairs of matching species, arising independently in separate lakes in Africa. In Lake Malawi, for example, there is a long and flat-headed species with a deep underbite that looks remarkably like an unrelated species that lives a similar lifestyle in Lake Tanganyika. There is another cichlid with a bulging brow and frowning lips in Lake Malawi with, again, an unrelated but otherwise extremely similar-looking cichlid in Lake Tanganyika. The same jaws, heads, and ways of living can be seen to evolve again and again.

The findings of evo-devo suggest that such parallels might in fact be expected. For cichlids are hardly coming up with new genetic solutions to eating tough snails as they each crank up the BMP4 or tinker with other toolkit genes. Instead, whether in Lake Malawi or Lake Tanganyika, they may be using the same genes to develop the same forms that provide the same solutions to the same ecological challenges. Why not, when even the beaked birds flying overhead are using the very same genes?

Evo-devo has even begun to give biologists new insight into one of the most beautiful examples of recurring forms: the evolution of mimicry.

It has long been a source of amazement how some species seem so able to evolve near-perfect mimicry of another. Poisonous species often evolve bright warning colors, which have been reproduced by nonpoisonous species or by other, similarly poisonous species, hoping to fend off curious predators.

Now in a new study of Heliconius butterflies, Dr. Mathieu Joron, an evolutionary biologist at the University of Edinburgh, and colleagues, found evidence that the mimics may be using some of the same genes to produce their copycat warning colors and patterns.

The researchers studied several species of tropical Heliconius butterflies, all of which are nasty-tasting to birds and which mimic one another's color patterns. Dr. Joron and colleagues found that some of the main elements of the patterns -- a yellow band in Heliconius melpomene and Heliconius erato and a complex tiger-stripe pattern in Heliconius numata -- are controlled by a single region of DNA, a tightly linked set of genes known as a supergene.

Dr. Joron said he and colleagues were still mapping the details of color pattern control within the supergene. But if this turned out to function, as researchers suspected, like a toolkit gene turning the patterns on and off, it could explain both the prevalence of mimicry in Heliconius and the apparent ease with which these species have been shown to repeatedly evolve such superbly matching patterns.

One of evo-devo's greatest strengths is its cross-disciplinary nature, bridging not only evolutionary and developmental studies but gaps as broad as those between fossil-hunting paleontologists and molecular biologists. One researcher whose approach epitomizes the power of such synthesis is Dr. Neil Shubin, an evolutionary biologist at the University of Chicago and the Field Museum.

Last year, Dr. Shubin and colleagues reported the discovery of a fossil fish on Ellesmere Island in northern Canada. They had found Tiktaalik, as they named the fish, after searching for six years. They persisted for so long because they were certain that they had found the right age and kind of rock where a fossil of a fish trying to make the transition to life on land was likely to be found. And Tiktaalik appeared to be just such a fish, but it also had a few surprises for the researchers.

"Tiktaalik is special," Dr. Shubin said. "It has a flat head with eyes on top. It has gills and lungs. It's an animal that's exploring the interface between water and land."

But Tiktaalik was a truly stunning discovery because this water-loving fish bore wrists, an attribute thought to have been an innovation confined strictly to animals that had already made the transition to land.

"This was telling us that a piece of the toolkit, to make arms, legs, hand and feet, could very well be present in fish limbs," Dr. Shubin said. In other words, the genetic tools or toolkit genes for making limbs to walk on land might well have been present long before fish made that critical leap. But as fascinating as Tiktaalik was, it was also rock hard and provided no DNA that might shed light on the presence or absence of any particular gene.

So Dr. Shubin did what more and more evo-devo researchers are learning to do: take off one hat (paleontologist) and don another (molecular biologist). Dr. Shubin oversees one of what he says is a small but growing number of laboratories where old-fashioned rock-pounding takes place alongside high-tech molecular DNA studies.

He and colleagues began a study of the living but ancient fish known as the paddlefish. What they found, reported last month in the journal Nature, was that these thoroughly fishy fish were turning on control genes known as Hox genes, in a manner characteristic of the four-limbed, land-loving beasts known as tetrapods.

Tetrapods include cows, people, birds, rodents and so on. In other words, the potential for making fingers, hands and feet, crucial innovations used in emerging from the water to a life of walking and crawling on land, appears to have been present in fish, long before they began flip-flopping their way out of the muck. "The genetic tools to build fingers and toes were in place for a long time," Dr. Shubin wrote in an e-mail message. "Lacking were the environmental conditions where these structures would be useful." He added, "Fingers arose when the right environments arose."

And here is another of the main themes to emerge from evo-devo. Major events in evolution like the transition from life in the water to life on land are not necessarily set off by the arising of the genetic mutations that will build the required body parts, or even the appearance of the body parts themselves, as had long been assumed. Instead, it is theorized that the right ecological situation, the right habitat in which such bold, new forms will prove to be particularly advantageous, may be what is required to set these major transitions in motion.

So far, most of the evo-devo work has been on animals, but researchers have begun to ask whether the same themes are being played out in plants.

Of particular interest to botanists is what Darwin described as an "abominable mystery": the origin of flowering plants. A critical event in the evolution of plants, it happened, by paleontological standards, rather suddenly.

So what genes were involved in the origin of flowers? Botanists know that during development, the genes known as MADS box genes lay out the architecture of the blossom. They do so by turning on other genes, thereby determining what will develop where -- petals here, reproductive parts there and so on, in much the same manner that Hox genes determine the general layout of parts in animals. Hox genes have had an important role in the evolution of animal form. But have MADS box genes had as central a role in the evolution of plants?

So far, said Dr. Vivian F. Irish, a developmental biologist at Yale University, the answer appears to be yes. There is a variety of circumstantial evidence, the most interesting of which is the fact that the MADS box genes exploded in number right around the time that flowering plants first appeared.

"It's really analogous to what's going on in Hox genes," said Dr. Irish, though she noted that details of the role of the MADS box genes remained to be worked out. "It's very cool that evolution has used a similar strategy in two very different kingdoms."

Amid the enthusiast hubbub, cautionary notes have been sounded. Dr. Jerry Coyne, an evolutionary biologist at the University of Chicago, said that as dramatic as the changes in form caused by mutations in toolkit genes can be, it was premature to credit these genes with being the primary drivers of the evolution of novel forms and diversity. He said that too few studies had been done so far to support such broad claims, and that it could turn out that other, more mundane workaday genes, of the sort that were being studied long before evo-devo appeared on the scene, would play equally or even more important roles.

"I urge caution," Dr. Coyne said. "We just don't know."

All of which goes to show that like all emerging fields, evo-devo's significance and the uniqueness of its contributions will continue to be reassessed. It will remain to be seen just how separate or incorporated into the rest of evolutionary thinking its findings will end up being. Paradoxically, it was during just such a flurry of intellectual synthesis and research activity, the watershed known as the New or Modern Synthesis in which modern evolutionary biology was born in the last century, that developmental thinking was almost entirely ejected from the science of evolution.

But perhaps today synthesizers can do better, broadening their focus without constricting their view of evolution as they try to take in all of the great pageant that is the history of life.

"We're still a very young field," Dr. Gilbert said. "But I think this is a new evolutionary synthesis, an emerging evolutionary synthesis. I think we're seeing it."

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GRAPHIC: Genetic Mimicry The Amazonian butterfly Heliconius numata (bottom row)is a polymorph, taking one of the seven forms shown. Each form of H. numata is a nearly perfect mimic of one of seven different species in the genus Melinaea (top row). A single, tightly linked set of genes appears to control the variations in the tiger-stripe wing pattern. Researchers suspect that this "supergene" helps explain both the wide range in patterns and the ease of mimicry.

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